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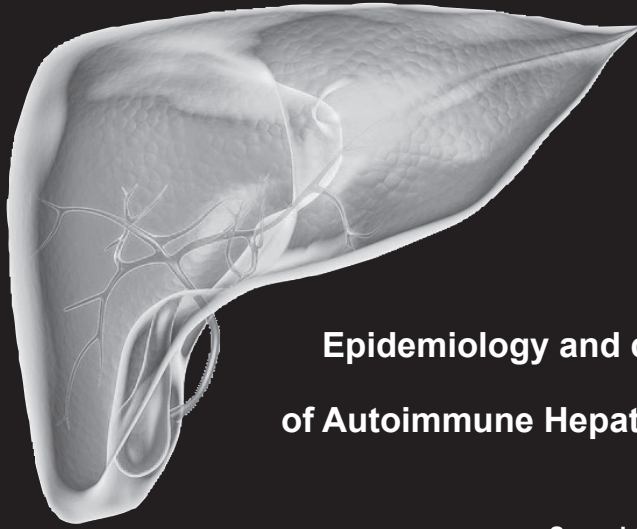
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Chapter 2

Epidemiology and clinical characteristics of Autoimmune Hepatitis in the Netherlands

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Abstract

Background and aims

Epidemiological data on Autoimmune Hepatitis (AIH) are scarce. We determined the clinical and epidemiological characteristics of AIH patients in the Netherlands (16.7 million inhabitants).

Methods

Clinical characteristics were collected from 1313 AIH patients (78% females) from 31 centres, including all eight academic centres in the Netherlands. Additional data on ethnicity, family history and symptoms were obtained by the use of a questionnaire.

Results

The prevalence of AIH was 18.3 (95% CI: 17.3-19.4) per 100,000 with an annual incidence of 1.1 (95% CI: 0.5-2) in adults. An incidence peak was found in middle-aged women. At diagnosis 56% of patients had fibrosis and 12% cirrhosis in liver biopsy. Overall, 1% of patients developed HCC and 3% of patients underwent liver transplantation. Overlap with primary biliary cirrhosis and primary sclerosing cholangitis was found in 9% and 6%, respectively. The clinical course did not differ between Caucasian and non Caucasian patients. Other autoimmune diseases were found in 26% of patients. Half of the patients reported persistent AIH-related symptoms despite treatment with a median treatment period of 8 years (Range 1-44 years). Familial occurrence was reported in three cases.

Conclusion

This is the largest epidemiological study of AIH in a geographically defined region and demonstrates that the prevalence of AIH in the Netherlands is uncommon. Although familial occurrence of AIH is extremely rare, our twin data may point towards a genetic predisposition. The high percentage of patients with cirrhosis or fibrosis at diagnosis urges the need of more awareness for AIH.

Introduction

Autoimmune hepatitis (AIH) is a chronic inflammatory liver disorder of unknown aetiology, which when left untreated can lead to hepatic failure and premature death¹. Women are affected more frequently than men and disease can develop in all age groups. The clinical spectrum is wide, ranging from absent or mild symptoms to fulminant hepatic failure and may vary among ethnic groups². AIH has features that resemble primary sclerosing cholangitis (PSC) and primary biliary cirrhosis (PBC) and overlap with these disorders are reported in 10-20% and 2-8% of cases, respectively^{3,4}. Associated concomitant autoimmune diseases in AIH have been reported in up to 40% of patients and may mask the underlying liver disease⁵.

There is no gold standard for the diagnosis of AIH and diagnosis is based on the combination of clinical and laboratory findings and histological abnormalities after exclusion of viral and other causes of hepatitis⁶. Diagnostic scoring systems have been developed that help to make the diagnosis in the majority of patients and are particularly useful for defining homogenous patient groups in the context of studies⁷. A simplified scoring system with four variables was recently developed that enhances its applicability in daily practice⁸.

There are few studies that have explored the prevalence of AIH. Older studies were often performed before the introduction of the diagnostic scoring system and have been biased to a certain extent by the fact that they do not rely on current standard criteria for patients' inclusion. Moreover, early studies did not exclude patients with chronic hepatitis C. Based on the available data, incidence of AIH is considered to be low, ranging from 0.08 in Japan⁹ to 3 per 100,000 in the United Kingdom¹⁰. In the current study we assessed the incidence and prevalence of AIH patients in the Netherlands 16.7 million inhabitants. In addition, we assessed the clinical spectrum and validity of diagnostic criteria in a large patient cohort of 1313 patients.

Material and methods

Patient population

Data for this retrospective study were retrieved from computerized or written medical records in 31 centres in the Netherlands, including 8 academic medical centres and 23 general district hospitals (Figure 1). Patients with AIH were identified based on information provided by co-investigators in the participating hospitals, by review of local AIH databases, and by searching the database for international disease classification codes. The search was done in different local diagnostic registers in gastroenterology and internal medicine departments, but not in

paediatrics. Adult patients who were diagnosed during infancy were likewise included. The medical records of AIH patients were traced back as long as possible. Patients included were diagnosed between 1967 and 2011.

The institutional review board of the VU medical centre and the review boards of all participating centres approved the protocol. All participating patients gave written informed consent.

Figure 1. Figure-map of The Netherlands with locations of the Hospitals included in this study



Diagnosis and application of diagnostic scoring systems

We included patients who had been diagnosed with AIH based on the combination of clinical, biochemical and histopathological criteria. In all patients alcohol-induced and drug related hepatitis had been excluded by clinical history. Viral hepatitis had been excluded by serological tests (hepatitis B and C) in all cases. Diagnostic scores were determined according to both the revised original criteria⁷ and the simplified criteria⁸. In approximately half of the patients, not all characteristics were available to calculate the revised original criteria.

Incidence and prevalence

To accurately determine the incidence and prevalence, the Amsterdam geographic region was studied as catchment area. In this region there are two academic hospitals and four regional hospitals. Many of the patients in the Academic Centres were referred from general district hospitals outside Amsterdam (50%). Patients who were referred from outside the region were excluded from this analysis.

Patient characteristics

As all data were collected from routine practice and diagnostic work-up, the available data could vary between participating hospitals. The following patient data were collected: gender, date of birth, date of diagnosis, characteristics of AIH (original and simplified criteria^{7,8}) at diagnosis and duration and type of therapy. In the eight academic centres it was documented if a liver transplantation was performed and when a patient developed a hepatocellular carcinoma (HCC). When available laboratory data collected included Alanine-aminotransferase (ALT), Immunoglobulin gamma G (IgG), Smooth muscle antibodies (SMA) and Antinuclear antibodies (ANA).

Details on portal, interface, overall inflammatory activity and on fibrosis/cirrhosis were retrieved from pathology reports when liver biopsy at diagnosis had been performed.

With regard to concomitant autoimmune diseases, the diagnosis of Inflammatory Bowel Disease (IBD) was based on clinical, endoscopic and histopathological features, diabetes mellitus on fasting blood glucose levels and thyroid disease by screening for TSH, T4 and when applicable thyroid antibodies. Diagnosis of overlap syndrome was made according to the diagnostic criteria of the involved diseases³. For PBC, these criteria comprised of anti mitochondrial antibody (AMA) titre higher than 1:80 and compatible histology. For PSC, these criteria generally were also based on histology and typical findings in radiological investigations (MRCP/ERCP). Human Leucocyte Antigens (HLA) typing was unavailable for all patients. Type of maintenance therapy was documented at the time the registers were searched.

Patients were asked to fill out a questionnaire assessing symptoms, family history, and ethnicity. In monozygotic and dizygotic twins disease concordance was studied.

Statistical analysis

Summary statistics for continuous variables were expressed as median with range (minimum-maximum). Summary statistics for categorical variables were expressed as numbers (percentages). Quantitative variables were described as means with their standard deviations or as medians with their range if not normally distributed. Categorical variables were summarized with frequencies and percentages. Depending on the distribution, parametric and nonparametric tests including T-test, Wilcoxon signed rank test and Sign exact test, were used to test for differences within and between groups. The Cox regression univariate and

multivariate analysis was used to test the relationship between patient characteristics. The trend in incidence was measured by the Cochran-Armitage Test for Trend. Two-sided P values less than 0.05 were considered statistically significant. Statistical analysis were performed using Statistical Package for Social Sciences (SPSS).

Results

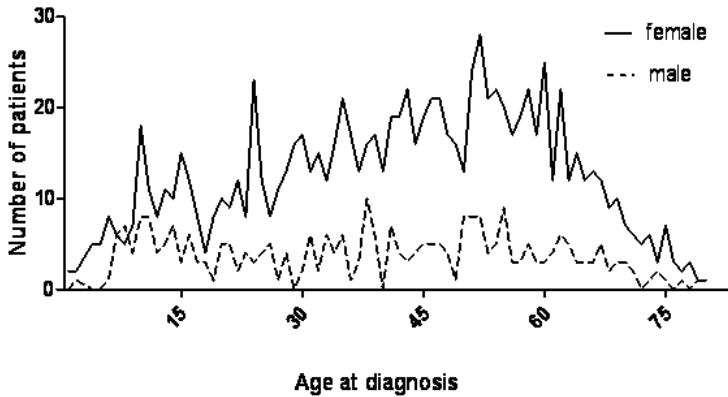
Experimental design and cohort characteristics

This retrospective analysis characterized the epidemiological characteristics of AIH in the Netherlands. A total of 1313 AIH patients were identified; among these 12% had been diagnosed under the age of 18 (Table 1). Median follow up time of this cohort was ten years (range: 0-44 years). There was a strong female preponderance; 1020 (78%) were females. The median age at diagnosis in females was 48 years (range: 5-87 years) and in men 43 years (range: 6-87 years; $P > 0.05$). An incidence peak in middle-aged women was found, with a smaller peak in adolescents (Figure 2). In men, no specific age-related incidence peak was observed.

Table 1. Patient characteristics in AIH and PBC/PSC overlap patients at diagnosis

Features	All patients	Pure AIH (n=1110)	Overlap PSC/PBC (n=193)	(n)
Gender (female/male); n	1020/293	865/255	142/51	1313
Median age males; y (range)	43 (6-87)	43 (8-87)	40 (6-82)	293
Median age females; y (range)	48 (5-87)	46 (8-87)	44 (5-84)	1020
Median ALT; IU/l (range)	299 (10-6667)	368 (20-6672)	255 (10-5523)	1295
Median IgG; g/l (range)	22 (6-42)	25 (8-42)	20 (6-28)	1206
Median ALP; IU/l (range)	149 (16-7107)	119 (16-6204)	263 (111-7107)	1270
SMA pos; n (%)	564 (52%)	530 (58%)	80 (46%)	1089 (912/175)
ANA pos; n (%)	610 (53%)	476 (49%)	88 (49%)	1152 (972/180)
Cirrhosis/fibrosis (biopsy); n (%)	128/580 (12%/56%)	108/480 (12%/55%)	20/100 (12%/58%)	1041 (869/172)
Decompensated liver cirrhosis; n (%)	66 (9%)	59 (9%)	7 (6%)	730 (657/115)
HCC; n (%)	8 (1%)	7 (1%)	1 (1%)	730 (657/115)
Liver transplantation; n (%)	25 (3%)	19 (3%)	6 (5%)	772 (657/115)

Abbreviations: ALT, alanine transaminase; IgG, immunoglobulin G; ALP, Alkaline phosphatase; SMA, smooth muscle antibodies; ANA, antinuclear antibodies; HCC, Hepatocellular carcinoma

Figure 2. Age at diagnosis of AIH in males and females

The population of the Netherlands consists of 16.7 million inhabitants, of which ~2 million (12%) are of non-Western descent (source: Statistics Netherlands; <http://www.cbs.nl>). This was similarly reflected in the patient cohort. Among the 564 patients who reported their ethnic background in the questionnaire, 501 (89%) were Caucasians, whereas 63 (11%) of patients reported another background, mostly of African (34%), Asian (16%), South American (16%) and European (11%) descent. It has been reported that disease manifestations of AIH may vary among ethnic groups ¹¹. However in this study cohort no significant differences could be observed in the frequency of cirrhosis and fibrosis, ALT levels, antibodies, disease scores according to the original and simplified criteria at presentation between Caucasian and non Caucasian patients ($P > 0.05$ for all parameters; data not shown).

Incidence and Prevalence

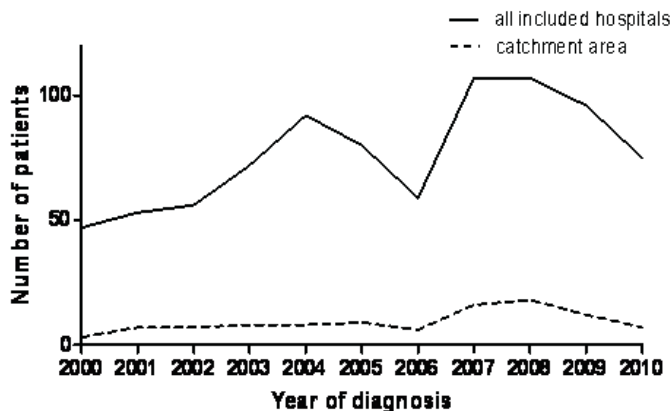
Incidence and prevalence figures were determined in the Amsterdam area, covering a population of 799,000 individuals (data: Statistics Netherlands) and extrapolated to the rest of the country. A total of 146 AIH patients was identified in the catchment area. According to these numbers the point prevalence in the Netherlands is 18.3 (95% CI: 17.3-19.4) per 100,000.

The incidence was calculated over a time span of 10 years. Between 2000 and 2010 an average of 77 (range: 47-107) new AIH patients were diagnosed in the participating hospitals. An average of 9 patients per year were diagnosed in the catchment area (Figure 3), resulting in an overall incidence in the Netherlands of 1.1 per 100,000 per year (95% confidential interval (CI): 0.5 – 2). Remarkably, there was a significant rise in incidence over the past 10 years in both the catchment area ($P < 0.01$) and in the overall cohort ($P < 0.01$).

The incidence and prevalence of AIH was further confirmed using another approach. Based on the hospital size (inferred from the number of beds and referrals), it is estimated that the 23

large hospitals included in this study (out of a total of 99 hospitals in the Netherlands) serve approximately 45% of the population. Extrapolating the number of patients identified in the participating hospitals to the total population would result in a prevalence of 18.7 per 100.000, very similar to the prevalence data tabulated from the catchment area.

Figure 3. Incidence rates of AIH between 2000 and 2010



Scores according to the revised original ⁷ and simplified ⁸ AIH diagnostic criteria

This analysis was performed in subgroups of patients with sufficient data to calculate the scores. Results of HLA typing were not available for our patients. The revised original criteria were assessed in 618 patients. The median post-treatment score at presentation in these patients was 19 points (range: 8-26 points). A total of 596 (97%) of patients fulfilled the diagnostic criteria for AIH; among these 442 (72%) patients could be classified as definite AIH and 154 (25%) as probable AIH. Among the 22 patients that did not fulfil the revised original criteria, 17 (77%) had evidence for an overlap syndrome, in particular with PBC (n=13). The fact that these patients did not fulfil the diagnostic criteria for AIH can be attributed to the fact that in case of AMA positivity 4 points are subtracted from the total score.

A total of 749 patients could be classified according to the simplified criteria. The median score was 6.4 points (range: 2-8 points). According to this classification 171 (23%) had probable AIH and 387 patients (52%) definite AIH whereas 191 (25%) patients did not fulfil the criteria for the diagnosis AIH (Table 2). Among the patients that did not fulfil the diagnosis AIH according to the simplified criteria 56 (29%) had an overlap with either PBC (n=32) or PSC (n=24).

In 618 patients parameters for both the revised original and the simplified criteria were available. Four hundred seventy of these patients (76%) fulfilled the criteria for either definite or probable AIH according to both scoring systems. A total of 110 patients (18%) with AIH according to the revised original criteria (79 with probable and 31 with definite AIH) did not fulfil the criteria for AIH according to the simplified criteria. *Vice versa*, 6 patients (5 probable and

one definite; 1%) fulfilled the diagnosis for definite or probable AIH according to the simplified criteria, but not according to the revised original criteria (Table 3).

Table 2. Disease scores according to the revised original and simplified criteria

		All patients (%)	Overlap with PBC/PSC
Revised original criteria * N=618	Definite AIH	442 (72%)	41 (9%)
	Probably AIH	154 (25%)	34 (22%)
	No AIH	22 (3%)	17 (77%)
Simplified criteria** N=749	Definite AIH	387 (52%)	48 (12%)
	Probable AIH	171 (23%)	15 (9%)
	No AIH	191 (25%)	56 (29%)

* Revised diagnostic scoring system of the International Autoimmune Hepatitis group⁷

**Simplified criteria⁸

Table 3. Comparison of the two scoring systems for the diagnosis AIH

		Patients with simplified criteria**			
		No AIH	Probable AIH	Definite AIH	Total
Patients with revised original criteria*	No AIH	16	5	1	22 (3%)
	Probable AIH	79	33	42	154 (25%)
	Definite AIH	31	68	343	442 (72%)
	Total	126 (20%)	106 (17%)	386 (63%)	618

* Revised diagnostic scoring system of the International Autoimmune Hepatitis group⁷

**Simplified criteria⁸

Laboratory values, antibodies and liver biopsy

Laboratory values

In this cohort, ALT levels were above ULN at diagnosis in 93% of patients, with a median ALT level of 299 IU/L (range: 10-6672) (Table 1). In 58% of patients ALP was not concomitantly elevated with ALP/ALT ratios < 1.5 in 79% of all AIH patients.

Total serum IgG was above ULN in 83% of the patients with 60% of patients displaying levels >1 G/L above ULN. The median IgG level was 22 G/L (range: 6-42).

In 36% of patients (n=473) all three conditions (ALT>ULN, ALP<ULN and IgG>ULN) were met at diagnosis.

Antibodies

ANA was measured in 1152 patients (88%) and SMA in 1089 (83%) at the time of diagnosis. Data on both antibodies could be retrieved from 1012 patients (77%). In 53% of patients ANA was positive and in 52% SMA positivity was found (Table 1). Both antibodies were positive in 380 (38%) of patients whereas 861 patients (85%) tested positive for at least one of these antibodies. Anti LKM1 were measured in 78 patients. Four patients tested positive, three of them being under the age of 18 years.

Liver biopsy

In 1041 (79%) patients diagnosis was further substantiated by a liver biopsy. Piecemeal necrosis (interface hepatitis) was reported in 903 patients (87%), plasma cells in 791 patients (75%) and in 163 patients (16%) rosettes were described. At diagnosis, 580 (56%) patients had fibrosis and 128 (12%) patients histological signs of cirrhosis (Table 1). Rosettes and interface hepatitis were significantly more present in a biopsy with concomitant fibrosis or cirrhosis *versus* a biopsy without fibrosis or cirrhosis ($P<0.01$ and $P=0.01$, respectively).

In an effort to link the presence of fibrosis or cirrhosis to biochemical parameters, we observed that patients with a normal IgG had significantly less fibrosis and cirrhosis than patients with elevated IgG levels at the time of diagnosis ($P<0.05$). No such association was found with ALT levels.

Concurrent auto-immune Disease

Concomitant auto immune diseases were observed in 335 patients (26%). These included 121 (9%) patients with thyroid disease, 63 (5%) with IBD, 52 (4%) arthritis and 27 (2%) with type I diabetes. Other reported autoimmune or immune mediated diseases included celiac disease, autoimmune hemolytic anemia, sarcoidosis, and multiple sclerosis. In this study 39 (3%) patients were diagnosed with more than one concomitant autoimmune disease. Significantly more women than men (27% vs 21%, $P=0.02$) had a concomitant other auto immune disease.

Overlap syndrome

Concurrent features of primary biliary cirrhosis or primary sclerosing cholangitis are frequently observed in AIH. In our AIH cohort 113 of 1313 patients (9%) were diagnosed with PBC and 80 patients (6%) exhibited an overlap syndrome with PSC. Patient characteristics are summarized in Table 1.

Biochemical and serological features of AIH were generally less pronounced in cases with overlap syndrome. Thus, mean ALT levels were lower in the group of patients with overlap syndrome (255 IU/L [range: 10-5525] *versus* 368 IU/L [range: 20-6672]; $P<0.01$). Similarly, the percentage of patients with ALT levels above ULN was lower in this patient category (87% *versus* 93%). In the overlap group 72% had IgG levels above ULN with a mean IgG level of 20 G/L (range: 6-28) *versus* 83% of patients without overlap with a mean level of 25 G/L (range: 8-42) ($P<0.01$).

SMA was positive in 46% of overlap patients *versus* 58% in the remaining AIH patients ($P=0.04$), whereas the frequency of ANA positivity did not differ between the two groups (~50%).

Self reported disease onset and symptoms

During the period the questionnaires were sent 38 (3%) patients have been diseased. A total of 564 (44%) of the 1275 patients, including 472 females (84%) and 92 males (16%) returned the questionnaire. The self reported information was collected a mean of seven years after diagnosis (range: 1-25 years). A symptomatic disease onset was reported in 288 (51%) of patients and included mainly jaundice (45%) and fatigue (51%) (Table 4). Forty-seven percent of patients reported persistent AIH-related symptoms despite the instituted immunosuppressive treatment. The most common symptoms were fatigue, joint pain and abdominal pain (Table 4).

Table 4. Self reported patient characteristics

Features	N = 564	Percentage (%)
Gender (female/male)	472/92	84/16
Ethnic background (Caucasian/other background)	501/63	89/11
Symptomatic onset disease	288	51
- fatigue	130	45
- joint pain	147	51
- abdominal pain	26	9
Symptoms despite treatment:	267	47
- fatigue	165	62
- fatigue and abdominal pain	30	11
- fatigue and joint pain	22	8
- other	50	19
First degree family member with other auto immune disease	236	42
Direct family member with AIH	2	0.3
Disease concordance in		
- monozygotic twins (n=1)	1	100
- dizygotic twins (n=5)	0	0

Familial occurrence

Data on familial occurrence and ethnicity were reported by 564 AIH patients. Among these, 236 patients (42%) reported a first degree family member with another auto immune disease; thyroid disease (20%), type I diabetes (14%) and arthritis (9%) being the most common. Two patients (0.3%) had a relative with AIH. One patient had a mother diagnosed with AIH and the other a cousin. In addition, there was one monozygotic twinpair in this cohort, and both individuals had AIH. Among the five dizygotic twins no disease concordance was found in any of the twin pairs (Table 4).

Medication

In 1284 patients maintenance treatment was documented. A total of 627 patients (49%) used combination therapy of prednison and azathioprine whereas 437 (34%) used monotherapy (either prednisone or azathioprine). Around one fifth of the patients (17%) was not using maintenance therapy. In these 220 patients without maintenance therapy 38 patients (17%) did not satisfy the simplified or the revised original diagnostic criteria. Patients using combination therapy had a higher mean diagnostic score at diagnosis (18.1 points according to the original criteria) when compared to patients on monotherapy (17.4 points) and patients without medication (14.2 points) ($P < 0.01$).

Clinical course

In the 8 academic medical centres in the Netherlands (including all liver transplantation centres) the clinical course of 730 patients (76% female) was documented. The median follow up time was 8 years (range 0-44 years). In these patients 120 (16%) developed portal hypertension, after a median of 17 months following diagnosis (range: 0 months-38 years). Sixty six patients (9%) developed decompensated liver cirrhosis after a median of 16 months (range: 0 months-38 years). In this cohort 8 (1%) patients were diagnosed with hepatocellular carcinoma (HCC), after a median of 6 years (range: 9 months-29 years) following diagnosis. Of the patients that developed a HCC, one patient had an overlap with PBC, none with PSC. Six of these patients had pre-existent cirrhosis.

Twenty five (3%) patients underwent liver transplantation after a median of 5 years (range: 8 months-30 years) following diagnosis. Five of these patients had an overlap with PSC, one with PBC. In addition, 14 patients (2%) were screened for liver transplantation and are still on the waiting list.

Discussion

Epidemiological studies in autoimmune hepatitis are scarce and the actual prevalence is currently unknown. Previous studies were hampered by the lack of uniform diagnostic criteria, were executed in either single centres or tertiary referral hospitals or consisted of mixed ethnic populations. In this large multi centre survey we aimed to overcome some of these limitations. In addition, we aimed to describe the clinical characteristics of AIH in a well defined large cohort of patients. Hereto, patient records from not only all 8 academic hospitals in the Netherlands were studied, as well as those from 23 regional non-academic institutions population and comprises the largest epidemiological AIH study so far. Also the catchment area for calculating incidence and prevalence included a combination of academic and non-academic hospitals and therefore presumably embodies a representative reflection of the

overall AIH patient population. A mean annual incidence of 1.1 per 100,000 per year and a point prevalence in the Netherlands of 18.3 per 100,000 as calculated from the catchment area was found. It should be noted that the incidence data presented here might slightly underestimate true incidence figures since paediatric patients, who account for approximately 10% of patients, were not included in this survey. In addition occasional patients may have been missed due to the fact that SLA and LKM-1 antibodies are not routinely measured.

Although there is some variation, presumably due in part to the considerations mentioned above, the findings presented in this study are comparable to studies from other European countries, including Denmark, Norway, Sweden, the United Kingdom and Spain. Incidence rates in these populations vary between 0.8 and 3 and prevalence data between 12 and 17^{10, 12-15}. A study from New Zealand reported an annual incidence of 2.0 cases of AIH per 100,000 and a somewhat higher prevalence of 24.5 cases per 100,000¹⁶. A study in well defined Alaskan native AIH patients reported a significantly higher prevalence of definite AIH of 35.9 cases per 100,000, with a particularly high prevalence in Southeast Indians. Unfortunately, no incidence data were presented in this study and it should be noted that this study involved a limited number of 56 patients in a catchment area of 100,312 individuals¹⁷. Finally in Japan, AIH appears to be considerably less frequent than in Western countries with an incidence estimated between 0.08 and 0.15¹⁸.

Of interest, a significant rise in incidence was seen in the Netherlands during the last decade and may indicate a true rise in incidence or, alternatively, increased awareness and diagnostic accuracy. These findings are in line with a previous observation from a single centre study in Spain¹⁴.

As expected, women were more affected than men with a sex ratio of 3.5:1 comparable to earlier studies¹¹. The age of first disease manifestation varies greatly from early life until old age. In our cohort the bimodal incidence pattern was only confirmed in women with a peak around the menopause¹¹. Whether the incidence peak around menopause relates to hormonal changes as suggested in other autoimmune diseases warrants further research¹⁹.

In our study population 97% of patients satisfied the criteria for probable or definite AIH. The small group of patients that did not meet the criteria included a high number of PBC overlap patients. Whilst the original criteria have a high sensitivity, the application of this scoring system is cumbersome in daily clinical practice and therefore a simplified scoring system was developed. Three retrospective studies indicated that this simplified scoring system had a somewhat lower yet acceptable sensitivity when compared to the original revised criteria²⁰⁻²². In this retrospective cohort however we observed that only 75% of patients with the clinical diagnosis AIH met the criteria for probable or definite AIH using this scoring system and in addition that almost one fifth of patients that could be classified as definite AIH according to

the revised original criteria did not fulfil the diagnosis AIH according to the simplified criteria. These findings indicate that at least in this large retrospective cohort the original revised criteria are superior to the simplified criteria. It should be noted that these findings are limited by the fact that comparison of these scoring systems was not the purpose of this study and that a significant number of patients could not be scored due to lack of data.

In all but its mildest form fibrosis is often present at diagnosis and with advanced disease bridging fibrosis and cirrhosis are often seen in AIH¹¹. In our study cohort more than half of the patients had fibrosis at diagnosis and in addition already 12% had cirrhosis. Similar or even higher cirrhosis rates have been observed in other studies, which indicates that disease has remained unrecognized for a significant period of time prior to diagnosis^{7, 15}. This study confirms earlier observations that the extent of histological damage is not related to the presence of symptoms²³ and thus urges the need for more awareness of the possibility of this disease even in asymptomatic patients.

Concurrent immune disorders are surprisingly common in AIH. One prospective study found that concurrent auto immune disease was present in 28 percent of 122 patients²⁴. The associated diseases may antedate the appearance of AIH or occur after the diagnosis has been established. The present study in a very large cohort of patients confirms these findings with thyroid disease being the most commonly associated disease. Similarly the co-existence of PBC or PSC in this large cohort of patients is at the same order of magnitude as reported earlier in smaller cohorts (reviewed by Rust et al²⁵).

There are virtually no reliable data on familial occurrence in AIH. Yet the occurrence of AIH in members of the same family is an infrequent observation. One study explored familial occurrence in a cohort of 219 patients and in this cohort 3 cases were identified where both mother and daughter were affected²⁶. There is an additional case report describing the occurrence of AIH in two sisters²⁷. In the present study we collected data from 564 patients by the use of a questionnaire. Co-occurrence of disease was identified in one mother-daughter pair and in addition in one third degree relationship. Interestingly the one monozygotic twin pair was concordant for disease, whereas no concordance was found in any of the 5 dizygotic twin pairs. Whilst these data may not appear impressive they all point, in addition to the established HLA association, towards a complex genetic predisposition, possibly with low penetrance²⁸. This notion is further supported by the high frequency of other autoimmune disease, both within patients as well as in relatives of patients, as noticed in our patient cohort as well as in another study²⁹.

The development of HCC was previously regarded as a rare complication of AIH. Three retrospective studies described the development of HCC in 1-4% of AIH cases³⁰⁻³². In a prospectively followed cohort the rate HCC development was substantially higher with 6.2% of all patients. This number was as high as 9.3% in patients who had cirrhosis at presentation³³. In the present study these numbers are of the same magnitude as the earlier retrospective studies.

AIH represents the indication for liver transplantation in 4-6% of adults in both the United states and Europe³⁴⁻³⁷. In our cohort 3% of AIH patients underwent liver transplantation whereas 2% were awaiting transplantation. This percentages is probably overestimated, while the data on transplantation were only collected from the academic centres and patients in need for a transplantation are transferred to these centres.

In conclusion, this study represents the largest nationwide study on the epidemiology of AIH so far. The findings presented in this study confirm that AIH is a relatively uncommon disease. The initial presentation of AIH varies widely and diagnosis can be supported by the revised original criteria and, to a lesser extent, by the simplified criteria. At diagnosis 12% of the patients already have cirrhosis and more than half of the patients fibrosis, which indicates a delay in diagnosis. No significant differences were observed in biochemistry, serologically and histology between Caucasian and non Caucasian patients. Although familial occurrence is uncommon, the available data point towards the role of genetic factors in disease predisposition. Overall 1% of AIH patients develops HCC and in three percent of patients liver a transplantation was performed. Prospective studies are warranted to substantiate the value of laboratory features, liver biopsy and to optimize the diagnostic criteria at diagnosis.

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